20. DISCUSSION AND SUMMING-UP

THE FINDINGS OF THE STUDY IN PERSPECTIVE

The very large amount of information made available by this study and set out in preceding sections has precisely the values and deficiencies which were anticipated when the project was first discussed. The findings give support to many views based on previous evidence. They are not compatible with some others. Some of the data presented are unique, perhaps in particular those relating to consanguinity of parents.

The study was intended to be exploratory, and to stimulate further work by defining some problems better and in so doing indicating where and how *ad hoc* studies might profitably be pursued. It is difficult for those responsible to judge how far these limited objectives have been achieved. However inadequate may be the comments and limited interpretations of the data which have been presented, this report, in conjunction with the Basic Tabulations by Centres booklet, provides, for interpretation by anyone interested, more detailed information in a form suitable for analysis than has ever previously been made available in respect of malformations occurring in a large series of births.

THE WAYS IN WHICH THE DATA HAVE BEEN PRESENTED

Throughout this report the data accumulated in the study have been set out in simple tabular form. There are large numbers of tables, and the information given in them is comprehensive. Further detail has been discussed in the text only where it seemed essential to explain or to stress what seemed of particular interest or importance. It was impracticable, before publication, to circulate the whole report and to seek comments from the organizers at all the centres. Under these circumstances, it was decided that the text should avoid, in so far as possible, controversial interpretations of their data.

The literature on congenital malformations is very large, and descriptions of many birth series with some specification of those malformed have been published. However, these accounts vary very greatly in size and few present the information in sufficient detail to permit even the simplest of comparisons with the present data. To have attempted a review of this literature would have required enormous effort, and would have increased greatly the size of the report.

The only large study in which the nature of the malformations was reported in any detail, and in which information on consanguinity was available, was the investigation sponsored by the United States Atomic Bomb Casualty Commission in Japan. The most complete information on this excellent work, in respect of the malformation data derived from all births in the populations, is in papers by Neel (1958) and Schull (1958). These authors set out the findings in 720 malformed infants occurring in 26 012 births in Hiroshima, 30 240 births in Nagasaki, and 7544 births in Kure, between 1948 and 1954. The over-all consanguinity rate was about 7%. References to these findings are made in several places in this report.

THE TYPES OF CONGENITAL DEFECTS RECOGNIZED AT BIRTH AND THEIR ETIOLOGY

Malformations recognized at birth are predominantly of types which are suspected to have complex genotypic as well as environmental contributions to their etiology, and the nature neither of the environmental nor of the genotypic contributions is understood. It has to be remembered in order to see these malformations in biological perspective (*a*) that those affected are the survivors of a much larger number of zygotes which were malformed and eliminated before or shortly after implantation or as recognized pre-28th week abortions; (*b*) that, as noted in section 2, there is ample evidence that the over-all frequency of malformations present at birth would, if all the children were followed up for a few years, be increased by about 50%, although the numbers "missed" at birth depend on the type of malformation and vary from zero upwards; (*c*) that the very small number of single-gene traits detected in this and other birth series reflects the small proportion of these traits which present as developmental defects recognizable by inspection of the child at birth; (*d*) that only a small proportion of infants who have gross chromosomal defects are detectable at birth by clinical methods only.

Quantitative aspects of these phenomena are reviewed in the report to the International Commission on Radiation Protection (1966). It is impor-

tant to realize that the remaining types of defects, which constitute a very high proportion of those reported in this study, are not associated with any specifiable genotypic or karyotypic situation, and, however we may speculate about the genotypic contribution and its interaction with environment, at best we are forced to postulate sufficiently simple genotypic and population genetic models and then to see how far the observed facts fit these models.

We know that insult to the embryo by radiation, rubella and possibly other virus infections and by certain chemical agents (including hormones) will determine malformations of these types and there is considerable time- as well as agent-specificity. However, we certainly have no means of identifying more than 1% or 2% of all these defects as being so caused.

There is, however, much to suggest that the environment is extremely important in determining many malformations. The variation by socio-economic class and the somewhat conflicting evidence for seasonal variation of neural tube defects have been most studied, mainly because the numbers of these are sufficiently large. It is doubtful whether, except possibly for harelip and cleft palate and for ulnar polydactyly, any variation by ethnic group can be substantiated. This is mainly because of the difficulty of separating out the effects of geographical location, social class and ethnic origins.

Most of these defects of complex etiology occur in sibs of index cases, with a frequency 5-10 times as great as that in the general population. As most, but not all, of them preclude the affected subjects having children or effectively limit their fertility it cannot be shown in these instances whether the frequency in other first-degree relatives of index cases is equally high.

There has been much controversy about the genetical theory involved and, in particular, about the interpretation of the excess mortality and the possibility of occurrence of malformations not readily recognized being due to homozygosity for single-gene mutations in the offspring of consanguineous parents. A "black-and-white" description of the basis of this controversy is that at one extreme the protagonists believe that almost all the excess mortality and malformation frequency is determined by homozygosity at specific loci, while at the other extreme there are those who consider that homozygosity at specific loci, although not always identifiable, is relatively unimportant. It is thought that the genotypes of importance in determining most developmental failures are determined at many gene loci and that the precipitating cause is often an unfavourable intra-uterine environment.

The controversies have been "spelt out" with some enthusiasm, particularly from one point of view by Schull & Neel (1965), and among other key references to the theory under discussion which should be consulted are the works of Lerner (1954), Dobzhansky (1955), Morton, Crow & Muller (1956), and Crow (1958). The very large number of consanguineous marriages reported in the present study makes a substantial contribution to the total information available on the relationship between consanguinity, perinatal mortality, and type and frequency of malformation.

SOME FINDINGS OF PARTICULAR INTEREST

Variations and associations of frequencies of neural tube defects and their relationships to consanguinity

The data on neural tube defects are discussed in section 4. There seems to be no doubt that there are real variations in the frequencies of anencephalus and of the other common neural tube defects in different parts of the world. This has long been known, and in particular, the remarkably high frequency of all these defects in Belfast has previously been reported. In this study Alexandria and Bombay also had very high frequencies.

The ten possible frequency comparisons between anencephalus alone, anencephalus with spina bifida, hydrocephalus alone, hydrocephalus and spina bifida, and spina bifida alone all show positive correlations over the 24 centres and these are all significant at least at a 5% level. This finding is of considerable interest and contradicts suggestions that some of the neural tube defect frequencies are negatively correlated. It also suggests that, whatever differing etiological factors there are for the different defects, there are some which are common to all. Apart from the findings of Polman (1951), no association of anencephalus or other neural tube defects with consanguinity had been reported. In this study there are significant associations between consanguinity and these defects in Alexandria and Bombay. Even when these two are excluded from the data, there is a non-significant association with consanguinity in the remainder. The numbers in Alexandria and Bombay are large and the associations highly significant. An explanation (other than that the relationship is causal) which occurs to the writers is that high consanguinity and neural tube defects may both be more common

to the lower socio-economic groups of mothers admitted to the hospitals in Alexandria and Bombay. However, it seems unlikely that this could explain all the association.

It would appear that, over the 22 centres for which the consanguinity data are available, there is a significant positive correlation between the frequency of neural tube defects and the estimated frequencies of dizygous twinning. No explanation can be offered for this phenomenon.

Harelip (G1), harelip and cleft palate (G2) and cleft palate (G3)

The high proportion of males in G1 and G2 and the correlation of frequencies of these two in various centres, significant at a 5% level, suggest a common etiology and support other evidence for such a supposition. In contrast, there is no excess of males in cases of cleft palate alone, and the correlations of G1 and G3, G2 and G3, and G1 + G2 and G3 are all negative and of borderline significance. This finding does not support the suggestion which has sometimes been made that, in spite of other evidence for heterogeneity in etiology, the frequency of cleft palate alone tends to be high in communities where the frequency of harelip and cleft palate is also high. It is noted that the disturbance of the sex proportion in the harelip and cleft palate group which is found when these are the only reported abnormalities is also found even when these are associated with other malformations, and so the cases were placed in the N group.

The frequencies of harelip and harelip and cleft palate are as high in several centres as those found in the Japanese study, when the comparisons are made either where these were the only defects or when they were associated with other malformations. It has to be remembered, however, that the Japanese data did not represent hospital cases only and the condition may be more common in hospital births. The frequencies in Chinese and Malays are high, and the relatively few data suggest a high frequency in European births in Johannesburg. There are also some centres in South America with relatively high frequencies. There is no evidence that the frequency is high in the offspring of mothers who were American Indians; however, the numbers are rather small.

The twinning data

When appropriate calculations are made it seems clear that (*a*) there is no significantly higher frequency of malformations in twins than in single-born infants; (*b*) the mortality and over-all malformation rates in monozygous twins are both higher than in dizygous twins and the more frequent death or malformation of both of monozygous twins does not fully account for this phenomenon.

There is confirmatory evidence of the homogeneity of the frequency of monozygous twinning over the range of centres, but highly significant heterogeneity of frequency of dizygous twinning so that the latter frequency is the predominant modifier of the over-all twinning rate. The dizygous twinning rate appears to be low in South-East Asia and very high in Alexandria and Belfast.

The consanguinity data

14 000 of the single-born infants in this study had consanguineous parents, and the over-all frequencies of consanguinity in these children varied from over 30% in Alexandria to less than 0.1% in Zagreb. These variations are so large that the summed data have to be interpreted with considerable care.

In families where the children were not malformed, there was strong evidence for a higher mortality (SB + LBD) in the offspring of consanguineous marriages, and it is demonstrated that the mortality is higher in closely related than in less closely related parents. No more detailed analysis of this mortality has been made, but the full data available to the authors are there for anyone who wishes to make the appropriate calculations and express the over-all detriment in terms of " lethal equivalents " or in other ways thought to be more appropriate or meaningful.

It is of interest to note that there was no contribution to the over-all increased mortality in the offspring of related parents in Alexandria, where both consanguinity and perinatal mortality were high. Presumably the amount of concealed inbreeding in Alexandria is high and the effects of inbreeding as identified in parents are masked by the high proportion of deaths primarily caused by poor socio-economic conditions.